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ION EXCHANGE RESINS AND NUTRITION

By Willard A. Krehl[1], Ph.D. and Robert W. Winters, M.D.[2]

Introduction

Although sodium and potassium are frequently relegated to obscure positions compared with the "glamor nutrients," the vitamins, their role in nutrition, particularly in controlling the water balance of the body, cannot receive too much emphasis. Water balance involves the maintenance of the total amount of water in the body, the proper distribution of water between cells and the extracellular fluid, and the volume of the circulating blood.

Low sodium diets are now established as valuable aids in the treatment of a variety of disorders. A number of problems, however, limit their practicability and general usefulness.

More accurate data are needed concerning the sodium content of various foods. These data are now becoming available due to the development of methods employing the flame photometer. There is need for making the low salt diet palatable and nutritionally adequate, since the patient may be eating the diet for months or years. The rice diet of Kemper (1) which has been used with some success in the dietary management of hypertension is a severely restricted, rather unpalatable diet that is low in calories, sodium chloride, fat, and especially protein. Some salt-substitutes have been tried with partial success, but these at best provide only a partial solution. Another approach is the reduction of salt intake through the special processing of salt-containing foods such as milk so that the sodium content is reduced.

The newest and one of the most promising ways of limiting the amount of physiologically available sodium for the patient is through the use of ion exchange resins.

These ion exchange resins, similar to those used for the purification and softening of water, are synthetic macromolecular organic compounds which undergo ionization. Other ions having the same electrical charge may replace those liberated from the resin. Thus an "ion exchange" is possible. Since the resins are not digested or absorbed the ion which becomes attached to the resin passes through the intestine and is removed in the feces.

When sodium is retained in the body, edema usually results and may be cleared by the increased elimination of sodium. A considerable amount of work has now been done with resins in this connection and is reviewed here. Certain of the fundamental aspects of edema formation are also considered.

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Physiological Anatomy of the Body Fluids

Water is the largest single component of the animal organism, comprising some 50 to 75% of the body weight, depending on the variable fat content of the body. Body water is divided into intracellular and extracellular compartments. The extracellular water is further subdivided into the intravascular portion which lies within the "vascular compartment" and the interstitial fluid which fills the spaces surrounding all of the various cells and tissues of the body. The intravascular fluid is circulated through the blood vessels and lymphatics. Water itself, as well as certain solutes, notably urea, is freely diffusible into all the cells of the body and throughout the vascular and interstitial compartments of the extracellular water. Such freely diffusible solutes contribute to the *total* osmotic pressure of all the fluids, but *do not* affect the distribution of the water *in vivo*. Other solutes—e.g. sodium, chloride, etc.—are not *freely diffusible* because of the peculiar semi-permeable character of the cell membrane and *do* contribute to the *effective* osmotic pressure. They are important in controlling changes in the distribution of water between the cells and the extracellular space.

Although the various subdivisions of the body fluids are isotonic with each other by virtue of the free diffusion of water, there is a marked difference between the composition of the intracellular and extracellular compartments. The extracellular fluid contains large amounts of sodium, chloride, and bicarbonate and only small amounts of potassium, calcium, magnesium, sulfate, and phosphate. The intracellular fluid on the other hand has a relatively high concentration of potassium, magnesium, and phosphorus.

The Physiology of Edema

Edema has been defined as an expansion in volume of the extravascular portion of the extracellular fluid. In composition edema fluid does not vary markedly from the normal interstitial fluid, it being essentially an ultrafiltrate of plasma. It is important to consider the nature of the forces which produce the dislocation of fluid into the interstitial space and the response of the kidney to this fluid maldistribution.

The mechanisms of control of fluid exchanges between the plasma and the interstitial fluid were described in 1908 by Starling (2). Given an endothelium (cell membrane) which is impermeable to proteins, passage of fluid from the blood and lymph vessels into the interstitial space is favored by the forces of capillary blood pressure and oncotic (colloidal osmotic) pressure of the interstitial fluid. Opposing this passage are the oncotic pressure of the serum proteins and the tissue turgor pressure. To these factors must also be added the important contribution of the lymphatic drainage.

Since the *effective* osmotic pressure of the extracellular fluid is dependent primarily on its content of sodium salts, it follows that when the sodium content of the extracellular fluid rises, the cells give up water and contract; and as the sodium level falls the reverse takes place. Sodium is then the means by which the distribution of water in the body is regulated.

The kidneys have a most important regulatory or conservative function as far as sodium is concerned. Sodium may be completely removed from the urine or may appear in considerable amounts. Water may likewise be variably treated so that a very concentrated or a very dilute urine may be produced. Obviously some water must always be expended in the excretion of those solutes (principally urea) which cannot be reabsorbed fully. Conservation of water by the kidneys can be obtained by maximum reabsorption of water and by maximum reabsorption of sodium salts.

The mechanisms controlling the reabsorption of sodium and water by the kidneys are complex. Certain hormonal mechanisms acting on the distal tubules of the kidney are recognized as important determinants of sodium and water excretion. The antidiuretic hormone of the posterior pituitary gland affects these cells so that there is maximal water reabsorption. The adrenal cortex through certain of its steroid hormones is known to increase sodium reabsorption by the tubular cells.

It is only reasonable to look to a distortion of the Starling equilibrium for an explanation of edema formation. The case of edema secondary to hypoalbuminemia (e.g. secondary to malnutrition, nephrosis, or liver disease) serves *par excellence.* The albumin of the serum is the great contributor to the colloidal osmotic pressure of that fluid. When its concentration is reduced, fluid will pass into the interstitial space thus causing a fall in circulatory volume. This decrease in plasma volume (or some function thereof) stimulates the adrenal cortex and the posterior pituitary gland to secrete their characteristic hormones. This in turn activates the distal tubule to increase sodium and water reabsorption (3). If the primary defect in the Starling equilibrium can be repaired—in this case, elevation of the colloidal osmotic pressure by albumin injections—the edema may be mobilized.

Although considerable disagreement exists among authorities as to the cause of cardiac edema, it makes very good physiological sense to consider its production in relation to a primary distortion of the forces of the Starling equilibrium. In this instance an elevation of the venous pressure produces an increase in capillary pressure and hence a displacement of fluid from the blood stream into the interstitial space. This results in a decreased plasma volume with the initiation of all the events discussed above.

By whatever mechanisms salt and water retention occur in congestive heart failure, it is certain that some or all of the sodium of the diet is retained

and that dietary restriction of sodium below that excreted in the urine will limit the extent of the edema and may produce a diuresis. Once an edema-free state is reached, it may be maintained by similar sodium restriction.

For many patients a satisfactory "salt-free" diet contains about one gram of salt per day. In others a more stringent restriction is necessary. The difficulty of preparing "salt-free" diets and their general unpalatability are well known. Hence, the ideas propounded by Dock (4) on the control of dietary sodium by ion exchange resins were greeted with great enthusiasm.

Principles of Ion Exchange

Introduction. Two nineteenth century agricultural chemists, H. S. Thompson (5) and J. T. Way (6), are usually credited with the first definitive study of the processes of ion exchange. They observed that when water soluble soil fertilizers such as ammonium sulfate or ammonium carbonate were added to soil, there was an apparent exchange of the ammonium ion for equivalent amounts of calcium ion—the calcium ion being released by some constituent of the soil. Although this work attracted a great deal of attention in agricultural circles, its widespread applicability was not realized until the present century, when the German chemist, Gans (7), provided the impetus for the industrial application of ion exchange principles; and Adams and Holmes in 1935 found that phenol and aromatic amines when condensed with formaldehyde gave insoluble synthetic resins with acidic and basic properties respectively. Polystyrene polymers containing acidic or basic groups have come into use more recently. Subsequently, these substances have been applied extensively to many problems of biology, chemistry and industry.

Theory of Ion Exchange. The present brief discussion of ion exchange will be limited generally to the cation exchangers and specifically to the two of these which are, medically speaking, the most important. (Extensive discussions are available elsewhere (8, 9)). These are the carboxylic acid and the sulfonic acid resins. These resins are polymers of aromatic hydrocarbons (benzoic or phenylsulfonic acids) which are linked together by the short carbon chains of the condensing agent (usually formaldehyde).

Both the carboxylic acid resins and the sulfonic acid resins carry acidic groups—namely, the COOH and the $-SO_3H$ groups. Under certain conditions the hydrogen of these groups may be exchanged for another cation in the surrounding solution:

$$\text{RESIN} - \text{COO}^- \text{Na}^+ + \text{H}^+ \text{A}^- \rightleftharpoons \text{RESIN} - \text{COO}^- \text{H}^+ + \text{Na}^+ \text{A}^-$$

It should be noted that this ion exchange reaction is reversible.

The several determinants of these ion exchanges are summarized as follows: First, resins have a certain selectivity of affinity for ions. In general,

among ions of the same valence, affinity correlates with the radius of the ion in aqueous solutions. Among ions of different valences, an increase in affinity correlates with increasing valence. These affinities for cations are independent of the type of anion in solution providing such anions do not form salts. Of course, concentration of the various cations is also important. Because the resins or ion exchangers have these different degrees of affinity for the different ions they have the essential property which permits *ion exchange.*

Second, resins have an optimal pH at which their maximal combining capacity is achieved. This is a function of the basic chemistry of the particular resin being considered. In general, the sulfonic acid resins have their optimal combining power at a relatively low pH, while the weaker carboxylic acid resins function optimally at an alkaline pH.

The "full" capacity of the resin—that is, the amount of cation exchanged by the resin as determined *in vitro*—is probably never realized under *in vivo* conditions. To cite an example, the carboxylic acid resin Amberlite IRC-50 under optimal *in vitro* conditions has a capacity of about 10 mEq of cation per gram of resin when the reaction is studied at pH of 10-11. At pH 7 this capacity drops to 6.2 mEq while at pH 6 it rapidly falls to 3.5 mEq. Considering other factors such as the relatively long reaction time for complete saturation, a reasonable *in vivo* capacity would be 2-3 mEq per gram with a reaction time of a few hours (10).

This failure to achieve full combining capacity in the body is due to imperfect realization of optimal pH conditions *in vivo,* and also to such factors as stability of the resin in the gastrointestinal tract, possible lack of homogeneity of the reactants in solution, limited duration of the reaction, and the possible interference of vitamins, proteins, lipids, steroids, etc.

Resins also show an interesting and characteristic swelling when placed in contact with ions in solution. In general, ions that cause greater swelling exhibit less affinity for the exchanger.

Studies in Experimental Animals

Various workers have studied the effects of resins on the mineral exchange of rats (4, 11, 12, 13) as well as dogs (14, 15, 16). In general, these studies have demonstrated that a considerable amount of sodium and potassium may be "taken up" by the resin and excreted in the stools. Concomitantly the animals usually decrease their urinary excretion of these cations and may retain a slight positive balance. The importance of the dietary composition as it relates to the ingestion of cations has been stressed, and it has been found that the ratio of sodium to potassium bound by the resins is usually equal to or greater than that in the diet.

Dock and Frank (17) in their review of the problem state that the up-

take by the resin approximates that which would be expected if final equilibrium were reached high in the intestine where dietary influence is evident.

When resins are fed with a diet practically devoid of sodium and potassium, negative balances may develop and the amount of potassium lost in the stools exceeds the amount of sodium lost. Under such conditions low muscle potassium and sodium values may develop and later low blood levels.

The low *in vivo* combining capacity of the resins as compared to their *in vitro* capacity has been confirmed in all of the studies; and the original figure given by Dock (4) of 0.9–1.3 mEq per gram of resin has been substantiated.

Clinical Studies and Results

A number of clinical investigators have published their results with cation exchange resins in edematous states incident to congestive heart failure, cirrhosis of the liver, renal disease, and chronic constrictive pericarditis.

The average patient may respond to resin therapy by a progressive weight loss sometimes to the previous non-edematous weight, or at least the patient may demonstrate no continued increase in weight or edema while receiving the resin. A number of cases have also been reported where patients not relieved by more conventional therapy responded to resins.

Klingersmith and Elkinton (18) have reported on the clinical effectiveness of cation exchange resins in a group of cardiac paients that well illustrates the results which may be expected. A total of 34 patients were studied, and of these, 27 received resin therapy for an average of 26.4 weeks. Patients were classified as follows: (a) Class I consisted of 16 patients who were refractory to intensive therapy with digitalis, low sodium diets (less than 0.5 gm. per day), frequent mercurials and restricted activity; (b) Class II consisted of 5 patients who were edema-free on low sodium diets (0.8–1.6 gm. per day), digitalis and mercurials; (c) Class III consisted of 6 patients who were maintained on digitalis but who reacted unfavorably to mercurials; (d) Class IV consisted of 7 patients, five of whom were either unable to tolerate resins and two on whom no follow-up data were available. Patients in the first three groups were placed on a mixture of ammonium : potassium resins (3:1 ratio), which was given in 15 gram doses three times a day.

The clinical effectiveness of the resins was appraised as follows: of the Class I patients, 13 of the 16 had a good result as indicated by loss of edema, a decrease in the frequency of mercurial administration and by a more liberal sodium allowance (0.8–1.6 gm. per day); of the Class II patients, all 5 had partial or complete replacement of mercurials; of the Class III patients, the resins were effective in mobilizing the edema in 5 of the 6 patients.

From their experience, these authors note that the resins do not replace the more conventional forms of therapy, but rather complement other methods.

They also point out that although the sodium intake may be increased, this increase is somewhat limited in that edema will usually reaccumulate if the intake exceeds 2.–2.4 gm. per day. However, if the sodium intake can be raised without prejudice to the patient's condition from less than 0.5 gm. to 0.8–1.6 gm. per day, the ease of preparing the diet is much greater.

These authors conclude with the following statement: "Like any other manipulation of a biochemical and physiological disturbance due to a diseased state, resin therapy of the edematous cardiac requires careful thought concerning the individual patient. But used in this way, and not as an infallible panacea, it should develop into a dependable item of the physician's armamentarium."

Biochemical Effects of Resins. The cation exchange resins are available in the hydrogen, ammonium, sodium and potassium forms, and individually or in combination increase the stool excretion of sodium and potassium.

The use of the ammonium or hydrogen cycle resins induce some interesting and important biochemical changes which need to be discussed here in connection with general resin therapy.

When fed in proper doses and with careful control of the sodium intake of the individual, the hydrogen or ammonium cycle resins can reduce sodium absorption from the intestine. This results in an increase in the stool sodium and a decrease in the urine sodium. Potassium usually follows sodium in these respects. After the exchange of hydrogen or ammonium ions for sodium or potassium in the gastro-intestinal tract, the liberated ions are absorbed into the blood stream along with the usual anions (chloride, phosphate, etc.). The ammonium ion so absorbed is promptly converted to urea by the liver with the release of a hydrogen ion.

Given adequate renal function, this absorption pattern usually produces a hyperchloremic compensated metabolic acidosis—the serum chloride rises, the serum bicarbonate falls, but there is little change in pH. The kidney reacts to these distortions in the acid-base equilibrium by (a) increased secretion of ammonium ion to go out with the strong anions and (b) secretion of a more acid urine so that the weaker anions may be excreted base free. In the absence of adequate renal function, these mechanisms may be deficient, and subclinical or clinical uncompensated metabolic acidosis may result.

Most observers report either a normal or slightly elevated level of serum sodium, while the serum potassium tends to be more frequently and more appreciably reduced. Potassium losses are attributable to a reduction of this cation from the intracellular compartment. Little change occurs however in the intracellular sodium.

The serum calcium level tends to be either normal or lowered. Tetany

or calcium deficit has been infrequently noted, although several cases have been reported (see below). It may be that the acidosis tends to protect against manifest tetany.

The similarity of the above biochemical changes secondary to resin therapy to those following treatment with ammonium chloride are obvious. Both agents produce a hyperchloremic metabolic acidosis, a condition generally considered to be advantageous in the treatment of edematous states. Both agents will potentiate the action of mercurial diuretics. In addition, the resins limit sodium absorption and therefore have a theoretical advantage. However, such an advantage demands more careful supervision so that acute hyponatremia with its attendant symptoms may be avoided.

Sodium, Potassium and Calcium Cycle Resins. These resins produce no significant changes in serum bicarbonate, chloride, sodium, calcium or water. Hyperkalemia is sometimes observed with the potassium cycle resin. With the sodium cycle material, there is an increase in the stool sodium and potassium; similar changes are seen with the potassium cycle resin. In contrast the calcium cycle resin is relatively inert, producing only very small changes in the stool content of either sodium or potassium. With the sodium resin there is a net positive balance, most of the sodium being retained extracellularly. The potassium resin likewise induces a positive balance of potassium, but most of this ion is retained within the cells (19).

Mixed Cycle Resins. A number of investigators, recognizing the dangers of potassium depletion with the acidifying resins (ammonium and hydrogen forms) have sought to combine these resins with a postassium cycle resin to circumvent this difficulty. Klingersmith and Elkinton (18) used a 3:1 mixture of ammonium to potassium carboxylic resin in the treatment of a number of patients with edema. Under this regimen the patients showed a trend towards hypokalemia, but only rarely were very low (less than 3.5 mEq/L) or very high (greater than 6.0 mEq/L) levels seen. It is also interesting that the general trend of the serum sodium levels in these patients was higher than before the resins were instituted. This may be related to the general improvement of these patients, since it is known that many edematous patients tend to have a light to moderate hyponatremia which reverts to normal in the non-edematous state. Under the combined resin treatment, these patients had increased serum chloride levels and decreased serum bicarbonate levels; neither, however, to any marked degree.

Peters et al (20) studied the effects of administering varying amounts of acidifying (hydrogen or ammonium cycle) and non-acidifying (potassium) cycle resins. They found that with a 1:1 combination (total dosage about 60 grams per day), the acidosis and hyperchloremia do not appear,

although the stool sodium is increased. This increase in the fecal sodium is not, however, of the extent that a similar amount of acidifying resin produces alone. With a 4:1 ratio of acidifying to non-acidifying resin, acidosis and hyperchloremia developed and the stool sodium increased. The data presented also demonstrates that such mixtures are a relatively inefficient method of providing the needed potassium when resins are used, since a fair amount of the potassium cycle resin appears in the stool and hence is not absorbed. They suggest that giving potassium as potassium chloride or as some other salt would not only be more efficient but also of less burden to the patient, since the latter are much easier to take than is the added bulk of the potassium cycle resin.

Side Effects of Cation Exchange Resins

There are several undesirable side reactions incident to the clinical use of ion exchange resins. Their low *in vivo* combining capacity necessitates the use of large doses. This material is not easy to take by mouth in large quantities, and many patients complain of the grittiness of the resins.

Irritation of the upper gastrointestinal tract is a common complaint and in part is referable to the exchange which occurs between the resin and the mucosal surfaces with the release of hydrogen ion locally. Nausea with or without vomiting may be due to a similar effect. These resins when wet swell considerably and after doses it is not surprising that patients feel satiated and anorexic. This effect has also been noted in animals. The bulk of the material causes the stools to be increased in size and firmness, and constipation is common. Abdominal cramps with or without diarrhea have also been reported. Generally these effects are minor and, if the patient is having a desirable effect from the resin, are tolerable. In other cases the resin may have to be discontinued temporarily, while in still others, these complaints are of such a degree that the resins have to be stopped permanently. Of the series of 34 patients reported by Klingersmith and Elkinton (18), 20 complained of one or more of the above gastrointestinal disturbances; therapy was interfered with temporarily in 11, permanently so in 5.

A polyuria resulting from resin therapy has been reported as well as an increase in the number of casts in the urine (21). This may be due to the acid urine which is excreted under resin administration. In the absence of renal disease, azotemia or other evidences of disturbed urinary function have not been observed. No change in the blood count was observed by Feinberg and Rosenberg (22) although an iron deficiency anemia has been seen in some patients.

The general tendency for hypokalemia has already been noted. Symptoms from this may not be evident although there are several cases (22, 23)

in which evidences of digitalis intoxication became evident when the patient developed hypokalemia. From the experimental work of Darrow and associates (23), it is known that potassium depletion may lead to alkalosis; this tendency is counterbalanced by the metabolic acidosis occurring in patients receiving resin by virtue of the chloride excess. However, there is always a potential alkalotic state in these patients if they are potassium depleted, and this could easily become manifest under conditions of further distortion to the composition of the body fluids. Kahn and Emerson (24) have reported hypokalemia, hypocalcemia and tetany in a patient receiving resin.

Recent investigators have recognized the danger of potassium depletion and have advised either supplementing the diet with extra potassium or administering resin partly in the potassium cycle. Caution in administering such materials to patients with chronic renal disease is recommended because of the inability of many such patients to excrete this ion.

Deficiencies of calcium, iron, manganese, magnesium and cobalt must also be considered in the use of ion exchange resins. A general tendency to hypocalcemia has been mentioned. In general, however, the losses of calcium in the stool have been less than originally anticipated (25), possibly because of the formation of complex salts in the gut. The problem of calcium deficiency has not been a serious one, although most authorities advise some form of calcium supplementation while the patient is on resin.

Theoretically, one might expect that deficiencies of other biologically important materials such as amino acids, thiamine, riboflavin, etc. might develop under resin therapy. Thus far no evidence of this has been seen, even in patients who have received resins for considerable lengths of time. It is noteworthy that the stool nitrogen does not increase appreciably in animals given resins; this is presumptive evidence against any serious nitrogen loss. Rats have been maintained on a diet containing 10% carboxylic acid resin for a year without signs of nutritional, reproductive or hematological abnormality; nor were any such abnormalities observed in any of three generations so maintained (14).

Natural Substances Having Cation Exchange Properties

Certain of the difficulties relating to the "resin type" ion exchangers such as gritty taste, bulk, gastrointestinal upset have invited the search for certain "natural" materials that have ion exchange potentialities. Alginic acid which is obtained from the giant kelp *(macrocystis pyrifer)* has shown definite cation exchange properties. Chemically, alginic acid is a polymer of anhydro-B-D-mannuronic acid. It has one free carboxy group per mannuronic acid residue and a theoretical cation combining capacity of 5.7 mEq

per gram. Ludwig et al (26) reported that "alginic acid possesses sodium and potassium ion exchange properties which compare favorably with those of a carboxylic type cationic exchange resin," and further state that, "the hydrophilic character of the sodium and postassium alginates may contribute to the elimination of fluid and cause laxation."

Although Ludwig et al (26) reported that alginic acid *in vitro* absorbs 4.2 mEq of sodium per gram at pH 7.6, a test of the cationic exchange properties of alginic acid made in human subjects (27) indicated that "the absorption of sodium by alginic acid is approximately one-fifth to one-sixth of the values reported for cation exchange resins." It was evident however that alginic acid was well tolerated.

Summary

As so often happens, the findings of fundamental research eventually find an application in medicine; such is the case with ion exchange resins. The highly developed theory of ion exchange led to the synthesis of "tailor made" large synthetic organic macromolecules with properties suited to the solution of specific problems.

When sodium is retained by the body, edema may often result. The increased elimination of sodium has been useful in this circumstance. It was not long before ion exchange resins were proposed to take up sodium and thus increase the fecal excretion of this ion. The resins offer particular utility here since they are not digested or absorbed.

The effectiveness of a resin in removing an ion from solution will be influenced by such factors as pH of the medium, the length of time of contact between the resin and the electrolyte, the concentration of the ions and by the particle size and porosity of the resin. Resins also have a greater affinity for some ions than for others.

Biochemically, the ammonium or hydrogen cycle resins produce a number of biochemical changes in the organisms—viz., an increase in the stool sodium and potassium, a decrease in the urinary content of these two ions, a hyperchloremic metabolic acidosis, sometimes a hypokalemia and occasionally a tendency toward hypocalcemia.

Undesirable side effects are frequent. Gastrointestinal symptoms of various types are quite common and sometimes necessitate temporary or permanent discontinuance of treatments.

In conclusion, however, it is evident that the resins provide a valuable additional therapeutic method of control of body water and electrolytes. The greatest practical use of these materials lies in allowing the patient on salt restricted diets more latitude in selection and greater palatability.

The frequency of biochemical abnormalities in subjects receiving resins

bespeaks caution in the use of materials without close laboratory and clinical control. The early detection and rectification of such serious conditions as hypokalemia must be realized else serious results will ensue.

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